The HepCar registry : report on a one-year registration program of hepatocellular carcinoma (HCC) in Belgium. What is daily practice in HCC?

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Abstract

Introduction : Due to a rise in HCV induced liver cirrhosis, hepatocellular carcinoma becomes more prevalent in Western European countries. The HepCar registry is an initiative in which patients with hepatocellular carcinoma, their treatment and follow up are registered.

Materials and Methods.

Belgian physicians were asked to report all new cases of hepatocellular carcinoma which were seen between January 2003 and December 2003. Reporting was done on a voluntary basis. Data reported were : demographic figures, the nature of the underlying liver disease, presentation characteristics of the tumour, laboratory findings and choice of therapy. Every six months, a reminder was sent to determine survival.

***Results :* 131 patients (94 male/37 female) were reported. Mean age was 63 years ± 13. Underlying liver disease was HCV (n = 54, 41%), HBV (n = 22, 17%), alcoholic liver disease (n = 39, 30%) and miscellaneous (n =16, 12%). Diagnosis of hepatocellular carcinoma was made by surveillance in 47 (36%) patients. After logistic regression, survival was 5 times better for patients inside the Milan criteria (one lesion less than 5 cm in diameter or less than 3 nodules each less than 3 cm in the absence of vascular invasion and metastasis).**

***Discussion :* Tumours inside the Milan criteria have a better survival. The majority of the patients have an underlying cirrhosis as background for the development of a HCC.** (Acta gastroenterol. belg., **2005**, 68, **403-411**).

Key words : Hepatocellular carcinoma, screening, survival, transplantation, treatment.

Introduction

Primary liver cancer is an important public health problem in the Far East and Sub-Saharan Africa where it accounts for one of the most frequent cancers due to endemic hepatitis B infection. In these regions, the mortality by hepatocellular carcinoma (HCC) is about 100 per 100 000 habitants (1,2). Conversely, HCC is a hitherto relatively rare cancer in Western countries. In Belgium, statistics from de National Cancer registry for the 1993-1995 period showed that the annual incidence of cancer classified as ICD 155 (International Classification of Disease – 7th revision) including primary liver, gallbladder and bile duct cancers was 4.9/100 000 in men and 5.2/100 000 in women (www.kanker-register.org). According to these statistics, the annual incidence of HCC is in a range of 2-3 per 100 000 habitants making of Belgium a low-incidence area for HCC.

In the United States, the incidence of histologically proven hepatocellular carcinoma increased from 1.4 per 100 000 for the period 1976-1980 to 2.4 per 100 000 for the period 1991-1995 (3). Epidemiological analyses have shown that hepatitis C virus infection accounted for most of this increase, while the rates of primary liver cancer associated with alcoholic cirrhosis and hepatitis B infection remained stable (4). In Belgium, it is likely that the increase in the incidence of HCC follows the epidemic of hepatitis C virus infection that occurred in late sixties and early seventies (5).

Surveillance for HCC in high-risk populations has become a popular clinical practice in Western countries. Nevertheless, it has up to now not been fully demonstrated that primary liver cancer ideally fulfils the accepted rules justifying surveillance. According to the World Health Organisation (6,7), surveillance programs should fulfil the following criteria :

1. The disease is recognised as an important public health problem.
2. Populations of high-risk patients can be identified.
3. The clinical stage of the disease is preceded by a period of latency when the disease is detectable.
4. Effective, safe and financially acceptable tools of early detection are available.
5. Curative treatment exists at an early stage resulting in survival improvement.

If it is widely accepted that surveillance for HCC fulfils the first 4 criteria, the last one, however, remains hotly debated.

Serum alfa-foetoprotein (αFP) and liver ultrasonography (US) are the usual tools of the surveillance for primary liver cancer in at-risk patients. Liver US is the most appropriate tool for surveillance of cirrhosis and early detection of small HCC. It is effective in this particular field, it is a non-invasive, non-expensive imaging technique and it is convenient for the patient. The impor-

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tance of the quality of the US examinations performed by the same, experienced operator has been pointed out by investigators who reported good results (8,9).

Several surveillance studies were disappointing showing a low rate (around 10-20 %) of resectability for small HCC identified during surveillance due to poor liver function, co-morbid medical conditions or technical reasons such as a tumour deeply placed or close to vital structures (9-12). Moreover, in some of these studies, when a HCC was detected, survival was not different between untreated and surgically treated patients (10,13). Trends in HCC survival in Europe (14) and in US (15) have shown a small improvement comparing the late seventies and early nineties with a 1-year survival improving from 8 % to 18 % (14) and 14 % to 23 % (15) respectively, but this could be attributed to the "lead-time bias" i.e. an artificial survival period corresponding to the interval from the point of detection by screening to the usual point of detection in the absence of screening. However these trials did not take into account the possibility of liver transplantation as a potential cure.

Nevertheless, a growing body of evidences strongly suggests that surveillance of patients with cirrhosis for the early detection of HCC could be effective in terms of survival prolongation at least in well selected cases. Moreover it seems unlikely that new randomised controlled trials will be put up to solve this issue.

As an alternative for randomised trials we put up a prospective registry (The HepCar Registry) where on a voluntary basis, physicians could report on new patients with hepatocellular carcinoma. The Hepcar Registry should :

- give an idea about the (reported) incidence of hepatocellular carcinoma in Belgium.
- give an idea about the proportion of incidental hepatocellular carcinoma's and carcinoma's found by screening.
- give an idea about the outcome and prognosis of hepatocellular carcinoma's and demonstrate if there is a difference in prognosis between incidental hepatocellular carcinomas and carcinomas found by screening.
- give an idea about other prognostic factors.
- give an idea about the habits according the treatment of hepatocellular carcinoma in Belgium.

Materials and methods

Inclusion of patients

Between January 1st, 2003 and December 31st, 2003 (total duration 12 months), Belgian gastroenterologists and hepatologists were invited to include in a prospective way patients with newly diagnosed HCC. In Belgium, most of the patients with HCC are taken care off by gastroenterologists and hepatologists. The participation was strong encouraged but remained on a totally voluntary basis.

When a patient was eligible for this registration, physicians were asked to fill in part I (cfr appendix) of the HepCar Registry (this could be found on internet) and to send it to the responsible person for this registry (HVV). After 6 months (and if the patient was still alive or not lost for follow up, after another period of 6 months), part II (cfr appendix) of the HepCar Registry was sent to the treating physician for completion.

The HepCar Registry asked for demographic figures, data about the nature of the underlying liver disease, presentation characteristics of the tumour, laboratory findings and choice of therapy according the local centre (cfr appendix). Since reference values for alkaline phosphatase and gamma glutamyl transferase were different between the different hospital clinical labs, these variables were filled in as 'times the upper limit of normal'. This initiative was announced on several occasions : Winter meeting Belgian Assocation for the Study of the Liver (BASL), December 2002 ; Spring meeting BASL 2003 ; BASL Presidential Letter in December 2002 and April 2003 ; and was put on internet (www.inwgen.be and www.basl.be).

Definition of HCC

HCC was defined in the presence of cirrhosis as a) characteristic tumour (arterial hypervascularization) of ≥ 2 cm on US or CT or Magnetic Resonance Imaging (MRI) and αFP level above 400 ng/mL or b) characteristic tumour (arterial hypervascularization) of ≥ 2 cm, assessed by two concordant imaging techniques (contrast enhanced US and/or CT and/or MRI) or by histological confirmation (16). In the absence of a characteristic tumour, histology was necessary to include the patient in the HepCar Registry.

In the absence of cirrhosis the diagnosis of HCC was made on the basis of : a) Characteristic tumour (arterial hypervascularisation) on US or CT or MRI and αFP level above 400 ng/mL or b) a biopsy of the tumoural lesion (16).

The Milan criteria were those as defined by Mazzaferro et al (17) : 1 lesion less than 5 cm in diameter or less than 3 nodules each less than 3 cm in the absence of vascular invasion and metastasis.

Statistical analysis

All data were put in an Excell sheet (Windows XP®) and statistical analysis was performed by MedCalc® (Version 7.0.1.0).

Variables influencing survival were analysed by step-wise logistic regression.

Parametric and non-parametric tests were used according to the distribution of the population. Differences in patient survival were calculated by the log-rank test and illustrated by the Kaplan-Meier survival curve. Multivariate analysis for factors influencing survival and spontaneous survival was performed by step-wise logistic regression. P-values of less than 0.05 were considered significant.

Results

Patient characteristics

131 patients (94 male (72%) / 37 female (28%)) in 14 centres were reported in the HepCar Registry database. Mean age was 63 years ± 13. Cirrhosis was present in 120 patients (92 %) and absent in 11 patients (8%). Aetiology of the underlying liver disease was : HCV (n = 54) (41%), HBV (n = 22) (17%), alcoholic liver disease (n = 39) (30%) and miscellaneous (n = 16) (12 %). The severity of the underlying liver disease was rather mild as illustrated by a mean MELD score of 9 ± 4. Diagnosis was made by surveillance/screening in 47 (36%) patients. In 32 patients (25 %), histological confirmation was obtained. In the rest of the patients the diagnosis was made by imaging and measurement of alfa foetoprotein only.

Fifty four (42 %) patients were within the Milan criteria. The median maximum diameter of the tumour was 40 mm (range : 5 mm-200 mm). The mean number of nodules was 2 (range : 1-10). Portal thrombosis was present in 35 patients (27 %). The presence of extrahepatic metastasis was observed in 14 patients (11%). Patients were asymptomatic in 45 % of the cases.

Treatment as chosen by the local physician was : listing for transplantation (cadaver or living) in 34 patients (26%), resection in 12 patients (9%) , percutaneous ethanol injection (PEI) in 7 patients (6%), radiofrequency treatment in 9 patients (7%), chemoembolisation in 11 patients (9%), I^{131} intra arterial treatment in 8 patients (6%), supportive or palliative care in 50 patients (38%). In patients listed for transplantation, additional treatment (PEI, radiofrequency, chemoembolisation, resection or I^{131} intra arterial treatment) was performed in 16 patients (49 % of those listed for transplantation). Two patients were delisted prior to transplantation due to progressive HCC disease. Sixteen patients were transplanted in the follow up period. Mean waiting time for this 16 patients was 120 days ± 101. Mean MELD score was 7 ± 3.

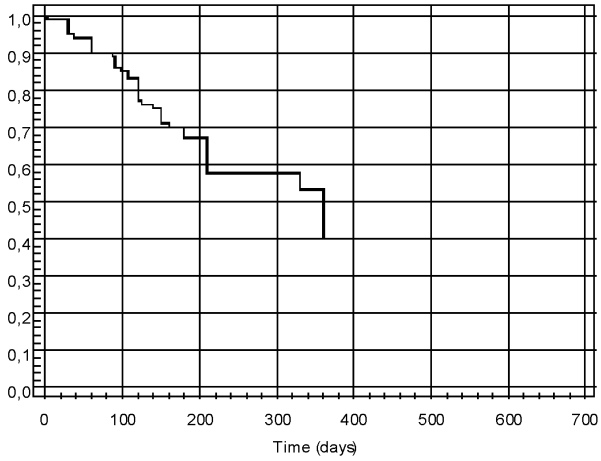

Fig. 1. — Kaplan Meier curve of overall survival.

Follow up could be obtained in 101 of the 131 patients (77 %). Sixty one patients (60 %) survived during a median follow up of 180 days (range : 2-630) (fig. 1).

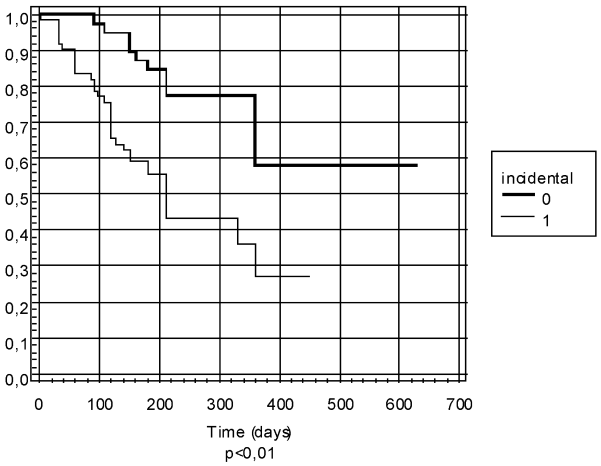

Fig. 2. — Kaplan Meier curve illustrating difference in survival between incidental (1) and screened tumours (0).

Table 1. — **Differences between patients with screened and incidental HCC**

	Screened HCC (n = 47)	**Incidental HCC (n = 8 4)**	**p-value**
Alkaline phosphatase (x ULN)	1 (0.5-12)	1.5 (0.5-9)	0.01
Gamma glutamyl transferase (x ULN)	2 (0.5-10)	4 (0.5-30)	< 0.001
Alcoholic liver disease (n(%))	8 (17%)	31(37%)	0.02
HCV related liver disease (n(%))	29 (62%)	25 (30%)	< 0.001
Inside the Milan criteria (n(%))	28 (60%)	26 (31%)	< 0.01
Max diameter of the tumour (mm)	30 (10-110)	45 (5-200)	< 0.01
Number of nodules	1 (1-10)	3 (1-10)	< 0.01
Presence of portal thrombosis (n(%))	6 (13%)	28 (33%)	0.01
Presence of metastasis (n(%))	0 (0%)	14 (17%)	< 0.01
MELD score (points)	8 ± 3	10 ± 4	0.01
Platelets (/µl)	139 (28-206)	174 (48-900)	< 0.01
Presence of symptoms (n(%))	13 (28%)	59 (70%)	< 0.001
Option to transplantation (n(%))	19 (40%)	15 (18%)	< 0.01
Number receiving palliative treatment (n(%))	8 (17%)	45 (54%)	< 0.001
Number of patients surviving (total n = 101) (n(%))	30 (60%)	31(40%)	< 0.001

Table 2. — **Variables with significant difference between HCC patients listed for transplantation and the other patients**

	Patients not listed for transplantation (n = 97)	Patients listed for transplantation (n = 34)	p-value
Age (years)	65 ± 12	57 ± 9	0.001
Alkaline phosphatase (x ULN)	1.5 (1-12)	1 (1-4)	0.001
Bilirubin (mg/dl)	1.3 (0.2-30.4)	0.1 (0.1-1)	< 0.001
Presence of HCV infection (n(%))	34 (35%)	19 (56%)	0.05
Incidental tumour (n(%))	69 (71%)	15 (44%)	< 0.01
Inside the Milan criteria (n(%))	32 (33%)	21 (62%)	< 0.01
Max diameter of the tumour (mm)	45 (5-200)	30 (10-100)	0.05
Presence of portal thrombosis (n(%))	31 (32%)	4 (12%)	0.04
Presence of metastasis (n(%))	14 (14%)	0 (0%)	0.04
MELD	9 ± 4	8 ± 3	0.03
Platelets (/µl)	186 (48-900)	103 (28-621)	< 0.001
Presence of symptoms (n(%))	61 (63%)	10 (29%)	0.001
Survivors (total n= 101) (log rank analysis) (n(%))	42 (40%)	19 (60%)	0.05

Incidental or screened tumours

Differences in incidental and screened tumours are illustrated in Table 1. Patients with HCC tumours found by screening had less advanced underlying liver disease, less advanced tumoural progression, more access to the therapeutic option of transplantation, were less likely to receive supportive treatment and had a better survival (fig. 2). Patients with alcoholic liver disease were more often found in the incidental group, whereas in patients with HCV, HCC was more often diagnosed by screening.

Characteristics of patients listed for transplantation.

In Table 2, the variables which differ significantly between patients listed for transplantation and the others are given. Patients listed for transplantation were younger, had lower MELD scores and less progressive HCC disease than patients not listed for transplantation. Patients listed for transplantation also had a better survival (fig. 3).

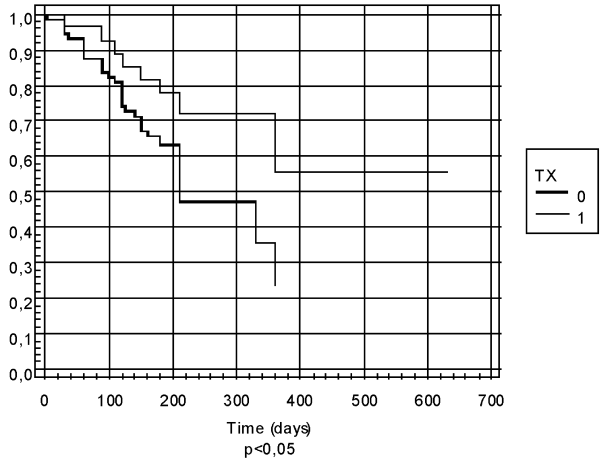

Fig. 3. — Kaplan Meier curve illustrating difference in survival between patients listed (1) or not (0) for liver transplantation.

Factors influencing survival

Table 3 lists the variables which had in monovariate analysis influence on survival. After multivariate analysis, only responding to the Milan criteria had influence on survival (OR 0.18 (95%CI : 0.06-058) (fig.4).

Discussion

The HepCar Registry was an initiative taken by the Belgian Association for the Study of the Liver (BASL) to get an idea about the behaviour and approach of HCC in daily practice. During the year of registration, 131 patients were announced through this registry. Not surprising the majority of the patients was male with a cirrhotic background. In a semi recent publication from a single centre out of Belgium, a higher proportion had an non-cirrhotic background (18). Although alcohol abuse remains the main cause for cirrhosis in Belgium (19), this aetiology is outnumbered by HCV in patients with HCC. This is in agreement with what was observed in a recent report of a Belgian single-centre observatory (19). As expected a majority of alcoholic patients was diagnosed incidentally, whereas in HCV patients the diagnosis of HCC was more often made through screening. One hundred thirty one HCC patients is about one half of the expected recruitment of all HCC in Belgium (National Cancer Registry). The 14 centres were not only academic hospitals but also regional hospitals as well in Flanders as in Wallonia. Thus we can expect that our recruitment was quite representative for the situation in Belgium.

HCC remains a disease with a dismal prognosis. At diagnosis, 6 out of 10 patients were outside the Milan criteria and were as such excluded for liver transplantation. In 4 out of 10 patients only supportive care was possible.

Reassuring is that in screened patients, more often tumours are found within the Milan criteria resulting in a better survival during the observed period and more

Table 3. — **Factors influencing survival (monovariate analysis)**

	Survivors (n = 61)	**Non-survivors (n = 40)**	**p-value**
Number of patients with an alfafoetoprotein > 400 ng/ml (n(%))	13 (21%)	17 (41%)	0.02
Alkaline phosphatase (x ULN)	1 (0.5-4)	2 (0.5-12)	< 0.001
Number of incidental tumours (n(%))	30 (49%)	31 (78%)	< 0.01
Number of patients inside the Milan criteria (n(%))	35 (57%)	6 (15%)	< 0.001
Max diameter of the tumour (mm)	30 (5-160)	60 (12-200)	< 0.001
Number of patients with portal thrombosis (n(%))	8 (13%)	21 (53%)	< 0.001
Number of nodules (n(%))	1 (1-10)	3 (1-10)	0.04
MELD	7 ± 3	10 ± 5	< 0.001
Number of patients with ascites (n(%))	14 (23%)	22 (55%)	< 0.001
Number of patients with varices (n(%))	20 (33%)	23 (58%)	0.01
Number of patients with symptoms (n(%))	11 (18%)	31 (78%)	< 0.00

often access to potential curative treatment options such as liver transplantation. Although a lead-time bias could be present, the better outcome in the time period observed for screened patients is hopeful. The median survival in our group was 180 days, which is shorter than reported by Grieco et al (median survival of 25.7 months)(20). However in their study, all patients were recruited from a surveillance programme and none of the tumours was incidental. The longer survival time in our trial and the trial of Grieco et al (20) are in favour of better survival probabilities in screened patients. Therefore an effort should be made to include more patients in surveillance programmes. Emphasis should be put on patients with alcoholic liver disease, although follow up of this group is hampered by social and psychological draw backs.

Differences in outcome between incidental and screened tumours could also possibly be related to the fact that incidental tumours behave more aggressively than tumours found by screening. However for tumours (screened or not) inside the Milan criteria, survival is identical. On the contrary for tumours outside the Milan criteria, screening results in a better survival probably by detecting smaller tumours than in the incidental group.

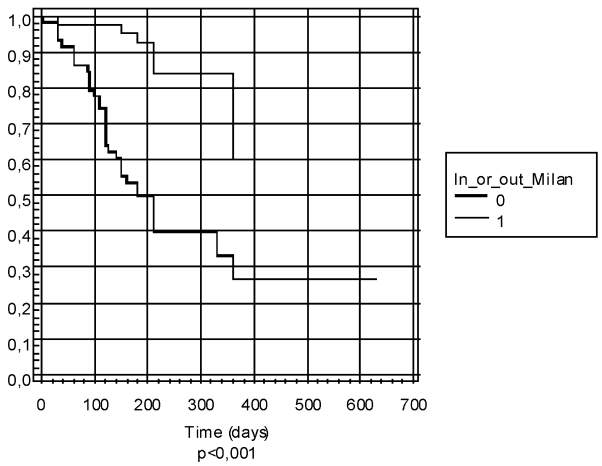

Fig. 4. — Kaplan Meier curve illustrating difference in survival between patients with HCC within (1) or outside (0) the Milan criteria.

Rather provocative it can be said that screening results in diagnosing more patients with HCC within the Milan criteria, but the survival benefit of screening is only observed in patients outside the Milan criteria.

In the entire group the Milan criteria remain a robust variable in predicting outcome. MELD score as a marker of underlying liver disease is not a predictive factor after multivariate analysis. These data underscore the lack of importance of the actual MELD score for HCC patients on the waiting list for a liver transplantation. At this moment only patients inside the Milan criteria can be listed for transplantation. In our cohort, some patients outside the Milan criteria were listed. Most of them only moderately differ from patients inside the Milan criteria (e.g. nodule of 60 mm in stead of 50 mm, or 4 nodules of 20 mm…). Some patients were listed as 'special request' patients. Most of these were young patients with no alternative treatment option. A 'special request' liver in the Eurotransplant region is a marginal liver discarded for transplantation in a classical indication, which can be used in 'marginal' indications.

On the other side, for patients inside the Milan criteria, there is no difference in survival during the observed period between listed patients for transplantation, patients having received a liver transplantation and patients in which transplantation was not chosen as a treatment option (data not shown). This can be attributed to the long tumour doubling time of some HCC tumours and the surgical related mortality. Longer follow up is necessary to observe a survival benefit for one of these groups. This means also that HCC patients within the Milan criteria do not earn, based on these findings, extra MELD points in the first 6-12 months of listing. At UNOS, patients with a single lesion smaller than 2 cm do not achieve more MELD points, however patients with more than 1 and less than 3 lesions smaller than 3 cm, get additional MELD points (21). Our data are in favour not to give additional MELD points for these patients.

As a conclusion, tumours discovered during surveillance and inside the Milan criteria have a better survival than other tumours. An effort should be made to motivate cirrhotic patients to participate in a surveillance programme. A longer follow up is necessary to draw

conclusions regarding the time moment of adding MELD points for patients on the waiting list for a liver transplantation.

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Appendix

Belgian Association for the Study of the Liver

HepCar Register (Section 1)

Identification :

Initials : …./….
Age : Birthday …./…./…….. (DD/MM/YYYY)
Gender : Male / Female
Race : Caucasian, African, Asiatic, Other
Nationality :

Cirrhosis :

Yes / No
Aetiology : HBV : Yes/No
HCV : Yes/No
Alcohol : Yes/No
hemochromatosis : Yes/No
Other : .....
Unknown : Yes/No
History of ascites : Yes/No (none/mild/severe)
Varices : Yes/No History of bleeding : Yes/No
History of encephalopathy : Yes/No

HCC diagnosis :

Incidental : Yes/No
Screening : Yes/No
Screening with alfa-foetoprotein : Yes/No
Ultrasound : Yes/No
Time of diagnosis ..../...../..... (DD/MM/YYYY)

HCC diagnosis confirmation :

Histological : Yes/No
Imaging : Ultrasound and Doppler : Yes/No
CT scan : Yes/No
MRI : Yes/No
Lipiodol CT : Yes/No
Angiography : Yes/No
Alfa-foetoprotein > 400 ng/ml : Yes/No

HCC symptoms :

Yes/No
If yes : Pain : Yes/No Jaundice : Yes/No
Anorexia : Yes/No Ascites : Yes/No
Weight loss : Yes/No Variceal bleeding : Yes/No

Biochemistry :

Alfa foetoprotein :	ng/ml	Alkaline phosphatase :	times Upper Limit Normal
Creatinine :	mg/dl	gamma GT :	times Upper Limit Normal
Albumin :	g/dl	Platelets :	/µl
INR :		Bilirubin :	mg/dl
PTT :	%		

Staging :

Milan/Bismuth criteria :
Number of nodules :
Maximum diameter of the greatest nodule : cm
Portal thrombosis : Yes/No
Metastasis : Yes/No
Bone : Yes/No
Lung : Yes/No
Brain : Yes/No
Peritoneal : Yes/No
Other :

Main first treatment(s).
Option to cadaveric liver transplantation : Yes/No
If yes : date of listing : ..../..../.....(DD/MM/YYYY)
Additional treatments : Yes/No
PEI : Yes/No
Transarterial chemoembolization : Yes/No
Radiofrequency treatment : Yes/No
Resection : Yes/No
I 131 Lipiodol treatment : Yes/No
Chemotherapy : Yes/No
Other :
Living related liver transplantation : Yes/No
If yes : date of operation : ..../..../..... (DD/MM/YYYY)
Additional treatments : Yes/No
If yes : which treatment : .....

Partial liver resection : Yes/No

Percutaneous Ethanol Injection : Yes/No

Radiofrequency Treatment : Yes/No

Transarterial chemoembolization : Yes/No

I 131 Lipiodol treatment : Yes/No

Systemic chemotherapy : Yes/No

Patient is only eligible for palliative treatment : Yes/No
Reason :.....

Other : .....

Treating physician :
Name : Hospital :
e-mail address :

Fax this document to 09 240 26 74 (Dpt of Gastroenterology, Ghent University Hospital).
You will receive a follow up questionnaire within a period of 6 months.
www.inwgen.be
Study coordinators : H. Van Vlierberghe, J. Henrion, N. Bourgeois, I. Borbath.

HepCar Register (section 2)

Concerning patient mentioned in section 1(Initials : ..../...., birthday : ..../..../.....), this is a follow up questionnaire after months.

Is patient alive : Yes/No

If the patient has died : date of death : ..../...../..... (DD/MM/YYYY)
Reason of death :
Tumour progression : Yes/No
Complications of the underlying cirrhosis : Yes/No
Other :

If the patient is alive :
Free of tumour : Yes/No
Partial response : Yes/No
Stable tumour : Yes/No
Progressive tumour : Yes/No

If the patient was listed for a cadaveric liver transplantation :
Patient still on the list : Yes/No
Patient received a transplant : Yes/No
Date : ..../..../..... (DD/MM/YYYY)
Patient was delisted : Yes/No
Reason : tumour progression : Yes/No

Evaluation of the cirrhosis at the moment of death or at the moment of the questionnaire if the patient is alive:

Alfa foetoprotein :	ng/ml	Alkaline phosphatase :	times Upper Limit Normal
Creatinine :	mg/dl	gamma GT :	times Upper Limit Normal
Albumin	g/dl	Platelets :	/µl
INR :		Bilirubin :	mg/dl
PTT :	%		

Ascites : none/moderate/severe
Varices : Yes/No
Bleeding: Yes/No

Fax this document to 09 240 26 74 (Dpt of Gastroenterology, Ghent University Hospital).
If the patient is still alive you will receive another questionnaire within 6 months.
Study coordinators : H. Van Vlierberghe, J. Henrion, N. Bourgeois, I. Borbath.